

Reata Enrolls First Patient with Pulmonary Hypertension Associated with Interstitial Lung Disease in LARIAT, a Phase 2 Study Examining Bardoxolone Methyl for the Treatment of Patients with Pulmonary Hypertension

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IRVING, Texas – January 5, 2016 – Reata has enrolled its first patient with pulmonary hypertension associated with interstitial lung disease (PH-ILD) into LARIAT, a Phase 2 study examining the safety, tolerability, and efficacy of bardoxolone methyl in patients with pulmonary hypertension (PH). The expanded LARIAT trial is now enrolling patients with PH associated with certain types of interstitial lung disease that are classified in the following categories:



- WHO Group 3 pulmonary hypertension patients with interstitial lung diseases:
 - Connective tissue disease-associated (CTD-ILD);
 - Idiopathic pulmonary fibrosis (IPF);
 - Nonspecific interstitial pneumonia (NSIP);
- WHO Group 5 pulmonary hypertension patients with sarcoidosis

Data recently presented at the [CHEST](#) meeting demonstrated that bardoxolone methyl improves functional capacity as assessed by the 6 minute walk test in WHO Group 1 PH (pulmonary arterial hypertension) patients who are already receiving stable, approved background therapies. The largest magnitude changes were noted in patients with connective tissue disease-associated PAH (CTD-PAH), and these patients typically respond less well to available therapies and have poorer overall outcomes. On the basis of these clinical data, as well as preclinical data demonstrating activity of bardoxolone methyl and analogs in several types of connective tissue disease and fibrotic pulmonary conditions, Reata has expanded its PH program into these interstitial lung disease patients.

"We are pleased to announce that we have quickly expanded our PH program into interstitial lung disease patients who have no approved therapies to treat their pulmonary hypertension," said Colin Meyer, M.D., Reata's Chief Medical Officer. "We hypothesize that bardoxolone methyl's novel mechanism of action of improving mitochondrial function and suppressing inflammation can translate to improved functional capacity in PH patients with interstitial lung disease."

About Bardoxolone Methyl

Bardoxolone methyl is an experimental, oral, once-daily antioxidant inflammation modulator (AIM) that has received orphan drug designation for the treatment of PAH by the US Food and Drug Administration. Bardoxolone methyl directly targets the bioenergetic and inflammatory components of PH. PH patients experience mitochondrial dysfunction, increased production of NF- κ B and related inflammatory pathways involved in ROS signaling, cellular proliferation, and fibrosis. Bardoxolone methyl, through the combined effect of Nrf2 activation and NF- κ B suppression, has the potential to inhibit inflammatory and proliferative signaling, suppress ROS production and signaling, reduce the production of enzymes related with fibrosis and tissue remodeling, and increase ATP production and cellular respiration.

About the LARIAT Study

LARIAT (A Dose-Ranging Study of the Efficacy and Safety of Bardoxolone Methyl in Patients with Pulmonary Hypertension) is a Phase 2 dose-ranging study examining the safety, tolerability, and efficacy of bardoxolone methyl in patients with PH on stable background therapy. To determine if bardoxolone methyl could complement approved PAH therapies, the Phase 2 study is designed to assess efficacy through exercise capacity.

Reata announced initial data from the LARIAT trial evaluating bardoxolone methyl in pulmonary arterial hypertension (PAH) patients at the annual meeting of the 2015 American College of Chest Physicians ([CHEST](#)) in Montreal, Canada.

All patients in the initial study cohorts were on stable doses of background PAH therapies at baseline and throughout the study. Efficacy analyses showed that bardoxolone methyl increased 6-minute walk distance (6MWD) in idiopathic PAH patients at doses of 2.5 to 10 mg through 16 weeks of treatment. PAH patients treated with bardoxolone methyl demonstrated a statistically significant mean increase in 6MWD compared to baseline of 22 m and a placebo-corrected difference of 21.4 m ($p = 0.037$). Notably, patients with connective tissue disease associated PAH (CTD-PAH), who typically experience less therapeutic benefit from approved PAH therapies, demonstrated a mean increase from baseline in 6MWD of 30 m and a placebo-corrected change of 44 m. This change may reflect the novel anti-inflammatory, metabolic, and mitochondrial effects of bardoxolone methyl.

Safety analyses from LARIAT demonstrated that bardoxolone methyl was well-tolerated with relatively fewer discontinuations in bardoxolone methyl-treated PAH patients compared to those who received placebo. No drug-related serious adverse events were reported, and the adverse event profile was manageable. Importantly, unlike previous observations in a subset of patients with advanced kidney disease, no fluid retention events or less severe manifestations of fluid retention were observed in the LARIAT PAH subjects. No meaningful or dose-related changes in blood pressure, heart rate, other measures of fluid status, and echocardiographic parameters were noted.

Reata completed an end of phase 2 interaction with the FDA in October, and the FDA concurred with Reata's proposal for an initial Phase 3 study in CTD-PAH patients using 6MWD as the primary endpoint. The primary endpoint will be assessed after 24 weeks of treatment. Reata plans to initiate this first Phase 3 study in the second half of 2016.

For more details on the LARIAT study visit <https://www.clinicaltrials.gov/ct2/show/NCT02036970>.

About Pulmonary Arterial Hypertension

PH is a multi-organ condition characterized by an abnormally high pressure in the network of arteries and veins that lead to and from the lungs due, in part, to narrowing of the pulmonary vasculature as a result of inflammation, remodeling, proliferation, and endothelial dysfunction. Mitochondrial dysfunction has also been implicated in PH. PH patients experience increased pressure on the right side of the heart, ultimately leading to ventricular failure and death. Although PH does not involve metastasis or disruption of tissue boundaries, it shares some features with cancer, including hyperproliferation and resistance to apoptosis, or programmed cell death, of vascular smooth muscle and other cells. Further, impaired energetics of skeletal muscle is a common feature of PH.

PH can be caused by a number of different underlying defects, which have been classified into five groups by the World Health Organization, or WHO¹.

PAH, like PH more generally, results in a progressive increase in pulmonary vascular resistance, which ultimately leads to right ventricular heart failure and death. PAH has a number of different etiologies, with approximately 72% of PAH cases being associated with either connective tissue disease, or CTD, or being idiopathic². Patients with CTD-PAH are generally less responsive to existing therapies and have a worse prognosis than patients with other forms of PAH³. In comparison to patients with idiopathic PAH, or I-PAH, patients with CTD-PAH have a higher occurrence of small vessel fibrosis and greater incidence of pulmonary veno-obstructive diseases⁴. CTD-PAH represents a subset of the PAH population with a significant unmet medical need.

Interstitial lung disease, or ILD, patients experience extensive pulmonary vascular remodeling, which ultimately leads to PH-ILD in approximately 30% to 40% of ILD patients⁵. PH-ILD falls under both WHO Groups III and V¹. PH-ILD patients have a one-year survival rate of approximately 63%, as compared to approximately 92% for ILD patients without PH⁶. Recent studies have demonstrated that mitochondrial abnormalities are key contributors to PH-ILD⁷. Currently, there are no therapies that are specifically approved to treat PH in interstitial lung disease patients.

About Reata Pharmaceuticals, Inc.

Reata Pharmaceuticals, Inc. is a clinical-stage biopharmaceutical company focused on identifying, developing, and commercializing product candidates that modulate the activity of key regulatory proteins involved in the biology of oxidative stress, mitochondrial function, and inflammation to address the unmet medical needs of patients with a variety of serious or life-threatening diseases. We focus on drugs with novel mechanisms of action that modulate important regulatory proteins, called transcription factors, that coordinate the cellular response to stressors by activating or suppressing the activity of many target proteins. The effects of AIM pharmacology have been documented in more than 200 scientific papers and are potentially relevant to a wide range of diseases.

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References

1. [Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, and Souza R. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;6:D34-41.](#)
2. [Badesch DB, Raskob GE, Elliot G, Krichman AM, Farber HW, Frost AE, Barst RJ, Benza RL, Liou TG, Tunner M, Giles S, Feldkircher K, Miller DP, McGoon MD. Pulmonary arterial hypertension: baseline characteristics from the REVEAL registry. CHEST 2010;137\(2\):376-387.](#)
3. [Rhee RL, Gabler NB, Sangani S, Praestgaard A, Merkel PA, Kawut SM. Comparison of treatment response in idiopathic and connective tissue disease-associated pulmonary arterial hypertension. Am J Respir Crit Care Med 2015.](#)
4. [Overbeek MG, Vonk MC, Boonstra A, Vosukyl AE, Vonk-Noordegraaf A, Smit EF, Dijkmans BAC, Postmus PE, Mooi WJ, Heijdra Y, Grunberg K. Pulmonary arterial hypertension in limited cutaneous systemic sclerosis: a distinctive vasculopathy. Eur Respir J 2009;34:371-379.](#)
5. [Behr J and Ryu JH. Pulmonary hypertension in interstitial lung disease. Eur Respir J 2008;31:1357-1367.](#)
6. [Lettieri CJ, Nathan SD, Barnett SD, Ahmad SA and Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006; 126: 746-752.](#)
7. [Cottrill KA and Chan SY. Metabolic dysfunction in pulmonary hypertension: the expanding relevance of the Warburg effect. European Journal of Clinical Investigation 2013; 43: 855-865.](#)